

(C) DATE:1995

(D) RELEVANT RESIDUES IN SEQ ID NO: 2: 1097-1118

(vii) SEQUENCE DESCRIPTION: SEQ ID NO:2:

TT GTG GTG AAC GAT AGA TGG AC

What is claimed is:

1. A method for generating phosphorothioate oligo mixtures comprising:
 - 1) growing a single-stranded recombinant DNA phage in modified media that uses thio-phosphate as a source of phosphate
 - 2) harvesting the single-stranded phage and purifying the DNA corresponding to the recombinant DNA insert
 - 3) fragmentation of the insert DNA such that oligo mixtures spanning the entire length of the segment are generated.
2. The method of claim 1 used to generate phosphorothioate ds DNA, ss DNA, and/or RNA by in vivo incorporation of thio-phosphate into nucleotide precursor pools.
3. The method of claim 1 used to generate ds DNA, ss DNA, or RNA partially substituted with phosphorothioate linkages by culturing cells in media consisting of a mixture of thio-phosphate and inorganic phosphate.
4. The method of claim 1 wherein the cells cultured in thio-phosphate media are of prokaryotic or eukaryotic origin.
5. The method of claim 1 using other derivatives of phosphate such as those substituted with one or more sulfur group, methyl group or other moiety.
6. A method for increasing the natural mutation rate of organisms, particularly, prokaryotes by culturing or growth in media utilizing thio-phosphate as a source of phosphorous.
7. The method of claim 6 used to selectively mutate phage or plasmid DNA comprising:
 - 1)several rounds of phage or plasmid amplification with host cells

cultured in the presence of thio-phosphate containing media

2) harvesting the phage or plasmid DNA after each cycle of amplification

3) infecting or transforming new host cells each cycle of amplification.

8. A method for stabilizing RNA in vivo and/or in vitro comprising:

1) the growth of prokaryotic or eukaryotic cells in media containing thio-phosphate as a source of phosphorous

2) the subsequent isolation of the RNA by rapid boiling, or organic extraction methods and/or RNA binding matrices.

9. The method of claim 8 where the introduction of thio-phosphate into multicellular organisms is accomplished by injection, digestion, or absorption.

10. The method of claim 8 used to maximize the accumulation of a desired protein product(s) comprising:

1) growing cells in thio-phosphate containing media

2) determining the optimal ratio of thio-phosphate to inorganic phosphate in the culture media

3) determining the optimal time point for maximum levels of protein synthesis.

11. The method of claim 10 wherein the cells used to generate the protein are prokaryotic or eukaryotic in origin.

12. The method of claim 10 wherein the protein is produced using a recombinant DNA expression vector.

13. The method of claim 10 wherein the enhancement of a protein or several proteins is used to increase the rate or yield of non-protein products such as antibiotics, chemical intermediates, organic acids, etc.